

Modelling molecular processes in weight loss

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Valorisation

Metabolic foundations of obesity and weight loss

Obesity is at epidemic levels, increasing worldwide in both developed and developing countries. Not only does obesity cause long-term physical stress on the body leading to joint pain and arthritis, it is also associated with the development of chronic illnesses such as type 2 diabetes mellitus, several cardiovascular diseases such as atherosclerosis, myocardial infarctions, arrhythmias and sudden cardiac arrests, and several cancers of organs and tissues associated with the gastrointestinal tract. Although weight loss via diet and exercise is one of the most successful methods of controlling obesity, many individuals regain about half of their lost weight shortly after the diet. In addition, our knowledge of the changes occurring inside our cells and organs is limited by both technology and the invasiveness of sampling procedures.

Due to these limitations, our understanding of the physiological changes in the human body had been limited for quite some time. An excellent example of this is the change in our understanding and perception of the adipose tissue over the past two decades. Previously, the adipose tissue was considered only as an energy storage organ for storing fats. As such, even though it was a major contributor to obesity, its role was considered a passive one. However, with advancement in technology, we have discovered the active hormonal and regulatory role that the adipose tissue plays in obesity, weight loss, and energy metabolism. The study presented in this thesis provides a glimpse of those changes in the adipose tissue in the case of weight loss in obese subjects. The study elucidates the role of adipocyte cellular metabolism in managing different nutrients for producing energy and provides a contrast of how the molecular processes differ between obesity and weight loss. These differences paint a picture of how obesity may arise on the molecular level and how cellular metabolism may affect weight loss, allowing future studies of a more targeted and personalised design, both in diet and exercise plans as well as drug development, to counter the effects of obesity and induce efficient weight loss. Additionally, the study presented here also pushes for a metabolism-based understanding of obesity and weight loss, allowing both researchers and the larger society to move beyond calorie counting when it comes to weight loss, and, in the future, personalise their own weight loss plans based on their understanding of their own metabolism.

Tools and resources for extended research

One of the problems facing the research community, and arguably the research domain in general, is the difficulty in replicating existing research. Many a times, produced data and reported results are difficult to use or replicate due to technological limitations, sampling biases and a general lack

of details of the procedure. To address these issues, the FAIR principles have been developed, promoting research and data to be Findable, Accessible, Interoperable and Reusable. Although not mandatory yet, these principles provide an abstract framework for research to be both available and useful to the wider research community, even across research domains. In compliance with these principles, the study presented in this thesis has been published with extensive supplementary materials. In addition, all computational pipelines and software used have been detailed with their versions and libraries in the respective research articles to support reproducibility, and any new or modified programming scripts have been provided as supplementary material.

Furthermore, the computational pipelines and analysis procedures utilised in this thesis have been constructed in a generalised manner. That is, the procedures can be used on similar data types in different biological settings to answer different research questions. Such approaches allow for the reusability and iterative improvement of the methodology in tandem with pushing the boundaries of science.

Marching towards virtual humans

Research is becoming increasingly costly and time consuming as we proceed with pushing the boundaries of knowledge and science. This produces a drain on the economy, as research cannot always promise a product or profit. This drain is especially true for medical sciences where a drug or treatment can take upwards of 15 years to develop, study, and trial for safety. However, medical sciences have also benefitted magnificently with the advancement of computers and digital technology. We have digitised our data to store millions of samples of thousands of studies, allowing unparalleled access and reusability. We are still tied to costly procedures, as we still require wet-lab analyses and experimentation to find medical solutions conclusively. To remedy this, computational modelling, simulation and analyses are taking precedence to cut down on time and cost. This thesis contains an application of this approach where a model of cellular metabolism was used due to technological limitations and a lack of available data. Such models are easy to manipulate and adapt for a variety of conditions, allowing researchers to simulate their experiments or procedures before spending limited and crucial economic resources. With advancement in computer engineering providing efficient and economical computational resources, the fields of theoretical and systems biology are steadily marching towards virtualising human systems and data to construct detailed simulations of humans, from molecular processes to personalities and behaviours. Such a technologies hold great potential for targeted and personalised medication for a fraction of the costs associated with current research and development procedures.